ZINC-OXIDE NANOPARTICLES AS FACILE CATALYST FOR RAPID SYNTHESIS OF 5-METHYL-4-(2-(3-METHYL-4-NITROISOXAZOL-5-YL)-1-ARYLETHYL)-1H-PYRAZOL-3-OLS IN AQUEOUS MEDIUM

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ABSTRACT

A Rapid and convenient protocol has been explored for the preparation of diversely functionalized pyrazol-3-ol compounds using zinc oxide nanoparticles as a heterogeneous catalyst. This protocol affords simple to operate, environmentally benign, mild and broadly applicable to synthesize a series of pyrazole-3-ols.

Keywords: Heterogeneous Catalysis, Zinc-oxide Nanoparticles, Multi-component Reaction, 3-Methyl-4-nitro-5-alkenylisoxazoles, Pyrazole.

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INTRODUCTION

Heterogeneous catalysis has significant advantages in industrial and academic laboratories owing to its environmental and economical applications.¹⁻⁵ Remarkably, heterogeneous nanoparticles having transition metal are very useful in catalysis due to its cost effective and recyclable nature. The zinc oxide nanoparticles (ZnO NPs) are highly significant transition metal containing nanoparticles because of its easy to carry, disposal character and non harmful nature.⁶⁻¹⁰ The current literature survey reveals that zinc oxide nanoparticles as heterogeneous catalysts are substantially important in catalysis.¹¹ Therefore the development of novel zinc oxide nanoparticles catalysed methods are highly desirable in organic synthesis.

Multicomponent reactions are highly important in synthetic organic chemistry as they offer quick formation of compounds in a single step via multiple bond formation.¹²⁻¹⁷ From green chemistry principles the improvement of new multicomponent reactions in aqueous medium for the preparation of privileged medicinally significant scaffolds are highly useful in drug discovery.¹⁸⁻²⁷ Furthermore, pyrazole containing compounds are ubiquitous in several natural products, active pharmaceuticals and agrochemical industries. Remarkably, pyrazoles and their analogues act as antimicrobials and oncology drugs.²⁸⁻³⁰ Specially, several significant commercial drugs having pyrazole framework, for instance celecoxib,³¹ lonazolac³² and rimonabant.³³ Synthesis of such pyrazole analogues using heterogeneous catalyst ZnO nanoparticles in aqueous medium is always highly significant.

Recently, many protocols have been explored for the preparation of pyrazole derivatives via Michael addition of 2-methylpyrazol-5-one to α,β -unsaturated carbonyls³⁴⁻³⁸ and β -nitrostyrenes.³⁹⁻⁴⁰ Recently, Meshram *et. al* reported multicomponent reaction to synthesize the pyrazole and isoxazole combined molecules.⁴¹ However, in this method they used toxic and non reusable piperidine as a catalyst at 80°C. From literature review, it is identified that no method is reported for the preparation of pyrazolone functionalized isoxazoles by one pot, three component reaction of hydrazine hydrate, ethylacetoacetate and 3-methyl-4-nitro-5-alkenylisoxazole using non toxic zinc oxide nanoparticles as a heterogeneous

catalyst. Hence an attempt is made to report a simple, convenient and mild protocol for the preparation of 5-methyl-4-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-arylethyl)-1*H*-pyrazol-3-ol.

EXPERIMENTAL

Materials and Methods

All chemicals and solvents are purchased from Avra Synthesis Pvt. Ltd. and Sigma Aldrich company, which are utilized without purification as received. Melting points are taken in a capillary and are uncorrected. ¹H-NMR and ¹³C-NMR are recorded on a Bucker 300 instrument and IR spectrum is recorded in KBr pellets on a Nicolet impact.

General Reaction Procedure for Preparation of Pyrazol-3-ol Derivatives

In a typical experiment the ethylacetoacetate **1** (1 mmol), hydrazine hydrate **2** (1 mmol), 3-methyl-4-nitro-5-alkenylisoxazoles **3** (1 mmol), ZnO (10 mol%) and water (3 mL) are taken in a 25 mL round-bottomed flask and stirred at 30°C for 15 mins. After the end of reaction (observed via TLC), it is filtered using sintered glass funnel, and the resulting solid is washed with hot H₂O and Et₂O and recrystallized in C₂H₅OH to achieve pure compound.

General Reaction Procedure for Synthesis of Zinc-Oxide (Zno) Nanoparticles

ZnO nanoparticles are prepared via precipitation protocol as reported in literature,⁴² and the prepared zinc-oxide nanoparticles are analyzed by powder-XRD, FT-IR and SEM.

Analytical Discussion

Compound 4a (Yellow Solid)

Yield 89 %; MP: 189-191 °C; IR (KBr, cm⁻¹): 3411 (R-OH), 2926 (R-CH₃), 2570 (=C-H), 1602 (C=C arom), 1517-1418 (N-O); ¹H-NMR (300 MHz, CDCl₃+DMSO-d₆): 7.48 (s, 1H), 7.37 (d, *J* = 7.3 Hz, 2H), 7.13-7.27 (m, 3H), 4.41 (t, *J* = 8.1 Hz, 1H), 4.01 (d, *J* = 8.1 Hz, 2H), 2.47 (s, 3H), 2.07 (s, 3H); ¹³C NMR (75 MHz, CDCl₃+ DMSO-d₆): 173.42, 160.11, 154.65, 142.57, 137.28, 127.85, 126.72, 126.00, 101.08, 37.38, 32.02, 10.95, 9.67; ESI-MS: *m/z*: 329 (M+H)⁺.

Compound 4c (Yellow Solid)

Yield 97 %; MP: 225-227 °C; IR (KBr, cm⁻¹): 3405 (R-OH), 2934 (R-CH₃), 1603 (C=C arom), 1514-1417 (N-O); ¹H-NMR (300 MHz, CDCl₃+DMSO-d₆): 7.88 (s, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.1 Hz, 2H), 4.31 (t, *J* = 8.1 Hz, 1H), 3.93 (d, *J* = 8.1 Hz, 2H), 3.74 (s, 3H), 2.45 (s, 3H), 2.03 (s, 3H); ¹³C NMR (75 MHz, CDCl₃+ DMSO-d₆): 172.41, 158.05, 156.19, 153.34, 135.35, 133.90, 128.30, 126.54, 111.98, 100.21, 53.34, 35.35, 30.90, 9.69, 8.42; ESI-MS: *m/z*: 359 (M+H)⁺.

Compound 4e (Colourless Solid)

Yield 92 %; MP: 204-206 °C; IR (KBr, cm⁻¹): 3319 (R-OH), 2928 (R-CH₃), 2604 (=C-H), 1605 (C=C arom), 1520-1491 (N-O); ¹H-NMR (300 MHz, CDCl₃+DMSO-d₆): 7.60 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.37 (t, *J* = 7.93 Hz, 1H), 3.98 (d, *J* = 8.1 Hz, 2H), 2.47 (s, 3H), 2.07 (s, 3H); ¹³C NMR (125 MHz, CDCl₃+ DMSO-d₆): 172.61, 159.31, 154.14, 140.93, 136.66, 130.88, 129.11, 127.84, 127.37, 100.16, 36.36, 31.40, 10.46, 9.13; ESI-MS: *m/z*: 379 (M+H)⁺.

Compound 4k (Colourless Solid)

Yield 85 %; MP: 177-179 °C; IR (KBr, cm⁻¹): 3346 (R-OH), 2925 (R-CH₃), 2624 (=C-H), 1602 (C=C arom), 1520-1422 (N-O); ¹H-NMR (300 MHz, CDCl₃+DMSO-d₆): 7.54 (s, 1H), 7.30 (s, 1H), 6.26 (t, *J* = 3.0 Hz, 1H), 6.09 (d, *J* = 3.2 Hz, 1H), 4.54 (t, *J* = 7.7 Hz, 1H), 3.95 (dd, *J* = 7.1, 14.9 Hz, 1H), 3.84 (dd, *J* = 8.6, 14.9 Hz, 1H), 2.50 (s, 3H), 2.09 (s, 3H); ¹³C NMR (75 MHz, CDCl₃+ DMSO-d₆): 171.84, 158.58, 153.86, 139.96, 136.47, 108.94, 104.31, 97.70, 29.86, 29.57, 10.11, 8.83; ESI-MS: *m/z*: 319 (M+H)⁺.

RESULTS AND DISCUSSION

The synthesized ZnO nanoparticles are characterized by powder-XRD, FT-IR and SEM as shown in Figures-1, 2 and 3.

Fig.-1: Powder XRD pattern of ZnO Nanoparticles

Fig.-2: FT-IR Spectra of ZnO Nanoparticles

Fig.-3: SEM Image of ZnO Nanoparticles.

Scheme-1: Optimization Studies

Initially, ethyl acetoacetate (**1**), hydrazine hydrate (**2**) and (*E*)-3-methyl-4-nitro-5-styrylisoxazole (**3a**) as model substrates are employed to test the desired three component reaction in aqueous medium (Scheme-1). The reaction has carried a reaction using 1.0 mmol of **1**, 1.0 mmol of **2**, 1.0 mmol of **3a**, 5mol% of

ZnO and H₂O 3mL at room temperature. After 60 mins, it is found that 65% of the product is formed (Table-1, entry 1). Later, it is carried reaction with 1.0 mmol of **1**, 1.0 mmol of **2**, 1.0 mmol of **3a** and water 3mL with diverse mol percentage i.e 10, 15, and 25 of ZnO as shown in above Table 1(entries 2-4). Reaction time also optimized and it is observed that the increase in yield with increase in mol percentage of ZnO (Table 1, entry 5 and 6). Finally, it is examined by using 1.0 mmol of **1**, 1.0 mmol of **2**, 1.0 mmol of **3a**, ZnO (10 mol %) and water 3mL at 35 °C for 15 mins and the required compound is formed by 95 % of yield (Table-1, entry 6). The structure of required compound is proved by using spectral analysis (¹H, ¹³C, IR and mass spectral data).

Table-1: Optimization Studies^[a]

S. No.	Zincoxide (ZnO) (mol %)	Reaction medium	Time (min) ^b	Yield (%) ^c
1	5	H ₂ O	60	65
2	10	H ₂ O	60	95
3	15	H ₂ O	60	94
4	25	H ₂ O	60	95
5	10	H ₂ O	30	95
6	10	H ₂ O	15	95
7	10	EtOH	60	50
8	10	MeOH	60	65

^aAll reactions are carried out with **1** (1 mmol), **2** (1 mmol), **3a** (1 mmol) and 3 mL H₂O.

^bReaction time in minutes. ^cIsolated yields of the Product.

From the observed reaction conditions, it is examined that the substrate scope of the present eco-friendly protocol. The protocol is proceeding well with various 3-methyl-4-nitro-5-alkenylisoxazoles as depicted in Table-2. The reaction gave good yields with 3-methyl-4-nitro-5-alkenylisoxazoles having electron withdrawing as well as donating groups on phenyl ring. The reaction is also carried out by using heterocyclic styryl isoxazoles **3k** and **3l** fruitfully as substrates.

Based on the earlier reports and above observations, a suitable pathway is proposed as shown in Scheme-3. Initially, ethylacetoacetate **1** and hydrazine hydrate **2** reacts to form 3-methyl-pyrazole-5-one (**A**). ZnO helps to form an enol intermediate from the 3-methyl-pyrazole-5-one (**B**). Which consecutively undergoes addition with (*E*)-3-methyl-4-nitro-5-styrylisoxazole (**3**) followed by rearrangement to form the corresponding compound **4** as shown in Scheme-2.

Scheme-2: Plausible Mechanism

CONCLUSION

An efficient and eco-friendly protocol has been developed for the preparation of diverse pyrazole derivatives via cyclization followed by Michael addition in water using ZnO as a heterogeneous catalyst. The method has excellent tolerance for diverse reactants. It is important to mention that the protocol not

require organic reaction medium. The pure form of product is isolated without using column chromatography which is an added advantage of this green protocol.

Table-2: Substrate Scope^[a]

^aReaction conditions: All reactions are performed by **1** (1 mmol), **2** (1 mmol), **3a** (1 mmol), ZnO (10 mol%) and 3 mL water. ^b Yield of the product.

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